

(FILE 'USPAT' ENTERED AT 11:15:06 ON 08 JUN 1998)

L1 90628 S NOTCH  
L2 373 S L1(P)DELTA  
L3 6 S L2(P) (PROLIFERAT? OR DIFFERENTIAT? OR CELL(W) FATE OR REG  
ENE  
E ARTAVANIS-TSAKONA/IN  
L4 310 S E4:E5  
L5 2 S L4 AND NOTCH

Set	Items	Description
S1	97115	NOTCH
S2	1083	S1(15N)DELTA
S3	230	S2(15N) (PROLIFERAT? OR DIFFERENTIAT? OR CELL(W) FATE OR CAN- CER OR REGENERAT?)
S4	78	RD (unique items)
S5	489	E1:E10, E16, E17
S6	326	S5 AND NOTCH
S7	88	S6 AND DELTA
S8	34	RD (unique items)

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File 164:Allied & Alternative Medicine(AMED) 1984-1998/Jan  
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File 358:Current BioTech Abs 1983-1998/Jun  
Royal Soc Chem & DECHEMA

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(c) 1998 Informania Ltd.  
File 624:McGraw-Hill Publications 1985-1998/Jun 04  
(c) 1998 McGraw-Hill Co. Inc

4/7/41 (Item 41 from file: 5)  
DIALOG(R)File 5:BIOSIS PREVIEWS(R)  
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10405480 BIOSIS Number: 96005480

IMPLICATIONS OF DYNAMIC PATTERNS OF DELTA AND NOTCH EXPRESSION FOR  
CELLULAR INTERACTIONS DURING DROSOPHILA DEVELOPMENT

KOOH P J; FEHON R G; MUSKAVITCH M A T

PROGRAM GENETICS, CELL DEV. BIOLOGY, DEP. BIOLOGY, INDIANA UNIV.,  
BLOOMINGTON, INDIANA 47405, USA.

DEVELOPMENT (CAMB) 117 (2). 1993. 493-507. CODEN: DEVPE

Full Journal Title: DEVELOPMENT (Cambridge)

Language: ENGLISH

**Delta** and **Notch** function are required for **cell fate** specification in numerous tissues during embryonic and postembryonic *Drosophila* development. **Delta** is expressed by all members of interacting cell populations within which fates are being specified and is subsequently down-regulated as cells stably adopt particular fates. Multiphasic expression in the derivatives of many germ layers implies successive requirements for **Delta** function in a number of tissues. At the cellular level, **Delta** and **Notch** expression are generally coincident within developing tissues. At the subcellular level, **Delta** and **Notch** are localized in apparent endocytic vesicles during down-regulation from the surfaces of interacting cells, implying an interaction consistent with their proposed roles as signal and receptor in cellular interactions during development.

4/7/42 (Item 42 from file: 5)  
DIALOG(R)File 5:BIOSIS PREVIEWS(R)  
(c) 1998 BIOSIS. All rts. reserv.

10110234 BIOSIS Number: 95110234

DLK A PUTATIVE MAMMALIAN HOMEOTIC GENE DIFFERENTIALLY EXPRESSED IN SMALL  
CELL LUNG CARCINOMA AND NEUROENDOCRINE TUMOR CELL LINE

LABORDA J; SAUSVILLE E A; HOFFMAN T; NOTARIO V

CENTER BIOL. RESEARCH, FDA., 8800 ROCKVILLE PIKE, BLDG. 29, BETHESDA, MD  
20892, USA.

J BIOL CHEM 268 (6). 1993. 3817-3820. CODEN: JBCHA

Full Journal Title: Journal of Biological Chemistry

Language: ENGLISH

Gastrin releasing peptide is mitogenic for mouse Swiss 3T3 fibroblasts and certain human small cell lung carcinoma (SCLC) cells but not for mouse Balb/c 3T3 fibroblasts. To identify new molecules associated with the gastrin releasing peptide-responsive phenotype, clones isolated from a differential cDNA library between Swiss and Balb/c 3T3 fibroblasts were used to screen for their expression in human SCLC cell lines. Using this approach, we have isolated and characterized human and mouse cDNA clones encoding a novel protein. This protein is a putative transmembrane protein belonging to the epidermal growth factor-like superfamily. In vitro transcription and translation studies detect a 42-kDa protein, in agreement with the size predicted from the translated cDNA sequence. This protein (termed **Delta**-like or **dlk**) is highly homologous to invertebrate homeotic proteins, including **Delta**, and **Notch**, the products of neurogenic loci involved in normal neural **differentiation** in *Drosophila*. **dlk** is expressed in tumors with neuroendocrine features, such as neuroblastoma, pheochromocytoma, and a subset of SCLC cell lines. However, its expression in normal tissues is restricted to the adrenal gland and placenta. These data suggest that **dlk** may be involved in

neuroendocrine differentiation and, because of its cellular location and restricted expression in normal tissues, it may be a potential therapeutic target in neuroendocrine tumors, particularly SCLC.

4/7/44 (Item 44 from file: 5)  
DIALOG(R)File 5:BIOSIS PREVIEWS(R)  
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7719734 BIOSIS Number: 90087734

LATERAL INHIBITION AND **CELL FATE** DURING NEUROGENESIS IN  
DROSOPHILA THE INTERACTIONS BETWEEN SCUTE **NOTCH** AND **DELTA**  
CABRERA C V

MARIE CURIE RES. INST., THE CHART, OXTED, SURREY RH8 0TL, UK.

DEVELOPMENT (CAMB) 109 (3). 1990. 733-742. CODEN: DEVPE

Full Journal Title: DEVELOPMENT (Cambridge)

Language: ENGLISH

A comparison of the patterns of expression of AS-C (T3) RNA and protein suggests that an important level of regulation occurs post-transcriptionally. First, when the RNA is abundant in the early embryo the protein is barely detectable. Later, the protein starts to accumulate in only a subset of the nuclei of those cells expressing the RNA. Only the cells in the subsets become the neuroblasts. This post-transcriptional regulation is suppressed in embryos mutant for the genes Notch and Delta; where all cells expressing RNA accumulate protein. These findings suggest that deployment of T3 protein expression is one of the causal factors that assigns specific fates to the neuroblast and, in consequence, a basis for the mechanism of lateral inhibition is proposed.

4/7/58 (Item 2 from file: 351)  
DIALOG(R)File 351:DERWENT WPI  
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009271449

WPI Acc No: 92-398861/199248

Human Notch and Delta DNA and protein sequences - used for study and manipulation of differentiation processes

Patent Assignee: UNIV INDIANA FOUND (INDV ); UNIV YALE (UYYA )

Inventor: ARTAVANIS-TSAKONAS S; BLAUMUELLER C M; FEHON R G; MUSKAVITCH M A  
T; REBAY I; SHEPARD S B; FEHON R; MUSKAVITCH M A; SHEPARD S

Number of Countries: 023 Number of Patents: 007

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Main IPC	Week
WO 9219734	A1	19921112	WO 92US3651	A	19920501	B	199248 B
AU 9219197	A	19921221	AU 9219197	A	19920501	B	199311
			WO 92US3651	A	19920501		
EP 576623	A1	19940105	EP 92911557	A	19920501	B	199402
			WO 92US3651	A	19920501		
JP 7503123	W	19950406	JP 92510668	A	19920501	B	199522
			WO 92US3651	A	19920501		
EP 576623	A4	19950118	EP 92911557	A	19920000	B	199545
AU 675203	B	19970130	AU 9219197	A	19920501	B	199713
US 5648464	A	19970715	US 91695189	A	19910503	B	199734
			US 94264534	A	19940623		

Priority Applications (No Type Date): US 91791923 A 19911114; US 91695189 A  
19910503; US 94264534 A 19940623

Cited Patents: 3.Jnl.Ref

Patent Details:

Patent	Kind	Lan	Pg	Filing Notes	Application	Patent
WO 9219734	A1	E	239			
				Designated States (National):	AU BR CA FI JP KR NO	
				Designated States (Regional):	AT BE CH DE DK ES FR GB GR IT LU MC NL SE	
AU 9219197	A			Based on		WO 9219734
EP 576623	A1	E		Based on		WO 9219734
				Designated States (Regional):	AT BE CH DE DK ES FR GB GR IT LI LU MC NL SE	
JP 7503123	W			Based on		WO 9219734
AU 675203	B			Previous Publ.		AU 9219197
				Based on		WO 9219734
US 5648464	A		116	Cont of	US 91695189	

Abstract (Basic): WO 9219734 A

A purified human Notch protein and fragments are new. Also claimed are (1) chimeric proteins comprising fragments of the human Notch protein joined to a heterologous protein sequence, (2) derivs. or analogues of the human Notch protein characterised by the ability in vitro, when expressed on the surface of a first cell, to bind to a Delta protein expressed on the surface of a second cell, (3) a pure fragment of Drosophila Notch protein comprising of the epidermal growth factor (EGF)-like repeats 11 and 12 of the protein, (4) a pure fragment of a Delta protein characterised by the ability in vitro when expressed on the surface of a first cell to bind a Notch protein expressed on the surface of a second cell, (5) a chimeric protein comprising fragments of the Delta protein joined to a heterologous protein sequence, (6) a pure fragment of Delta protein which is characterised by the ability in vitro when expressed on the surface of a first cell to bind a second



Delta protein or fragment expressed on the surface of a second cell, (7) a pure fragment of the Serrate protein, which is characterised by the ability in vitro, when expressed on the surface of a first cell to bind to a Notch protein expressed on the surface of a second cell, (8) DNA (I) encoding a human Notch protein, or complementary to it, (9) a vector comprising (I), (10) a recombinant cell contg. the vector of (9), (11) an antibody which binds to human Notch protein but does not bind the Drosophila Notch protein and (12) DNA encoding (a) a protein sequence homologous to both a Serrate protein and a Delta protein and (b) a second amino acid sequence which is not homologous to either a Serrate protein or a Delta protein.

USE - The nucleic acid and amino acid and antibodies can be used for the detection and quantitation of mRNA for human **Notch** and **Delta** and adhesive molecules, to study its expression, to produce human **Notch** and **Delta** and adhesive sequences, for the study and manipulation of **differentiation** processes.

(Dwg.0/25

Abstract (Equivalent): US 5648464 A

A novel substantially purified protein comprises an amino acid sequence encoded by the 267, 574, or 295 nucleotide DNA sequences given in the specification, which is able to be bound by an antibody to a human Notch protein but not to a Notch protein of another species.

Dwg.0/24

Derwent Class: B04; D16

International Patent Class (Main): C07K-014/435; C12N-015/12; C12P-021/02

International Patent Class (Additional): C07K-007/10; C07K-013/00;  
C07K-014/47; C07K-015/12; C12N-005/10; C12N-015/63; C12P-021/00;

4/7/60 (Item 2 from file: 357)  
DIALOG(R)File 357:Derwent Biotechnology Abs  
(c) 1998 Derwent Publ Ltd. All rts. reserv.

143356 DBA Accession No.: 93-01408 PATENT  
Human, Drosophila and Xenopus chimeric Notch protein and Delta protein and  
Serrate protein expression - for use in manipulation of  
differentiation; toporythmic gene DNA sequence  
PATENT ASSIGNEE: Yale-Univ.; Indiana-Univ.Found. 1992  
PATENT NUMBER: WO 9219734 PATENT DATE: 921112 WPI ACCESSION NO.:  
92-398861 (9248)  
PRIORITY APPLIC. NO.: US 791923 APPLIC. DATE: 911114  
NATIONAL APPLIC. NO.: WO 92US3651 APPLIC. DATE: 920501  
LANGUAGE: English

ABSTRACT: The following are new: (1) chimeric proteins comprising fragments  
of purified human Notch protein (HNP) joined to a heterologous protein  
sequence (PS); (2) derivatives or analogs of the HNP able (in vitro) to  
bind to a Delta protein (DP) expressed on the surface of a second cell;  
(3) a pure fragment of Drosophila Notch protein (DNP) (or a Xenopus  
Notch protein) comprising the epidermal growth factor-like repeats 11  
and 12 of the protein; (4) a pure fragment of a DP able to bind to a  
Notch protein expressed on the surface of a cell; (5) a chimeric  
protein comprising fragments of the DP joined to a heterologous PS; (6)  
a pure fragment of DP able to bind to a DP or fragment expressed on the  
surface of a cell; (7) a pure fragment of a Serrate protein able (in  
vitro) to bind to a Notch protein expressed on the surface of a cell;  
(8) DNA (I) encoding HNP, or complementary to it; (9) a vector  
comprising (I); (10) a recombinant cell containing (9); (11) an  
antibody binding to HNP but not binding to the DNP; and (12) DNA  
encoding a PS homologous to both a Serrate protein and a Delta protein,  
and a second PS not homologous to either a Serrate or Delta protein.

4/7/65 (Item 4 from file: 399)  
DIALOG(R)File 399:CA SEARCH(R)  
(c) 1998 American Chemical Society. All rts. reserv.

111091521 CA: 111(11)91521v JOURNAL  
Molecular genetics of Delta, a locus required for ectodermal  
differentiation in Drosophila  
AUTHOR(S): Alton, Althea K.; Fechtel, Kim; Kopczynski, Casey C.; Shepard,  
Scott B.; Kooh, Pamela J.; Muskavitch, Marc A. T.  
LOCATION: Dep. Biol., Indiana Univ., Bloomington, IN, 47405, USA  
JOURNAL: Dev. Genet. (N. Y.) DATE: 1989 VOLUME: 10 NUMBER: 3 PAGES:  
261-72 CODEN: DGNTDW ISSN: 0192-253X LANGUAGE: English  
SECTION:  
CA203003 Biochemical Genetics  
CA212XXX Nonmammalian Biochemistry  
IDENTIFIERS: Drosophila gene Delta mol genetics, mutation Notch Delta  
Enhancer of split, phenotype interaction Notch Delta Espl development,  
ectoderm differentiation neurogenic gene Drosophila  
DESCRIPTORS:  
Embryo,ectoderm...  
differentiation of, of Drosophila melanogaster, role of neurogenic gene  
product in  
Gene and Genetic element,animal, Notch...  
for neurogenic protein, of Drosophila melanogaster, effect of gene  
dosage on female wing phenotypes and interaction with Dl and E(spl)  
loci in relation to  
Gene and Genetic element,animal, Enhancer of split...  
for neurogenic protein, of Drosophila melanogaster, interaction with  
gene Dl and N proteins of  
Gene and Genetic element,animal, Delta...  
for neurogenic transcripts involved in ectodermal differentiation, of  
Drosophila melanogaster, mol. genetics of, interaction with Notch and E  
(spl) loci in relation to  
Development,nonmammalian...  
gene Delta expression during, of D. melanogaster, multiple transcripts  
and interaction with gene Notch and E(spl) products of  
Mutation...  
in Delta locus of Drosophila melanogaster, definition of  
multifunctional locus by, interallelic complementation in relation to  
Complementation,genetic, interallelic...  
in Delta locus of Drosophila melanogaster, mol. genetics of  
Drosophila melanogaster...  
neurogenic loci Dl and E(spl) and N of, interaction of products of  
Protein sequences...  
of homologous regions in blood-coagulation factor IX and Drosophila  
Delta DlZM protein  
CAS REGISTRY NUMBERS:  
9001-28-9 62229-50-9 Delta gene protein DlZM of Drosophila melanogaster  
homol. to

4/7/73 (Item 8 from file: 434)  
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci  
(c) 1998 Inst for Sci Info. All rts. reserv.

12599071 Genuine Article#: LZ432 Number of References: 39  
Title: THE PLEIOTROPIC FUNCTION OF DELTA DURING POSTEMBRYONIC DEVELOPMENT  
OF DROSOPHILA-MELANOGASTER

Author(s): PARODY TR; MUSKAVITCH MAT

Corporate Source: INDIANA UNIV, DEPT BIOL, PROGRAM GENET CELL &  
DEVBIOL/BLOOMINGTON//IN/47405; INDIANA UNIV, DEPT BIOL, PROGRAM GENET  
CELL & DEVBIOL/BLOOMINGTON//IN/47405

Journal: GENETICS, 1993, V135, N2 (OCT), P527-539

ISSN: 0016-6731

Language: ENGLISH Document Type: ARTICLE

Abstract: Analysis of the development of Delta (Dl) temperature-sensitive mutants pulsed at restrictive temperature during larval and pupal stages reveals multiple phenocritical periods during which reduction of Dl function affects viability and development of adult structures. Dl function is required during the third larval instar for post-pupal viability and during the first day of pupal development for viability through eclosion. Dl function is required biphasically for the development of sensory bristles. Earlier pulses lead to bristle multiplication and later pulses lead to bristle loss. The exact intervals during which multiplication and loss are induced vary for different bristles. Dl function is also required for development of most, if not all, cell types in the retina. Different pulses result in reduction in eye size, scarring, and glossiness, as well as multiplication and loss of interommatidial bristles. We also define intervals during which Dl function is required for aspects of leg and wing development. Phenocritical periods for Dl function are temporally coincident with those previously reported for Notch (N), consistent with the hypothesis that the proteins encoded by Dl and N interact throughout development to assure correct specification of cell fates in a variety of imaginal tissues.

4/7/74 (Item 9 from file: 434)  
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci  
(c) 1998 Inst for Sci Info. All rts. reserv.

12370727 Genuine Article#: LF042 Number of References: 40  
Title: DELTA-FUNCTION IS REQUIRED FOR BRISTLE ORGAN DETERMINATION AND  
MORPHOGENESIS IN DROSOPHILA

Author(s): PARKS AL; MUSKAVITCH MAT

Corporate Source: INDIANA UNIV, DEPT BIOL, PROGRAM GENET CELL &  
DEVBIOL/BLOOMINGTON//IN/47405

Journal: DEVELOPMENTAL BIOLOGY, 1993, V157, N2 (JUN), P484-496

ISSN: 0012-1606

Language: ENGLISH Document Type: ARTICLE

4/7/75 (Item 10 from file: 434)  
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci  
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12275334 Genuine Article#: KZ423 Number of References: 44  
Title: MOUSE NOTCH - EXPRESSION IN HAIR-FOLLICLES CORRELATES WITH CELL FATE  
DETERMINATION

Author(s): KOPAN R; WEINTRAUB H  
Corporate Source: FR HUTCHINSON CANC RES CTR/SEATTLE WA/98104  
Journal: JOURNAL OF CELL BIOLOGY, 1993, V121, N3 (MAY), P631-641  
ISSN: 0021-9525

Language: ENGLISH Document Type: ARTICLE

Abstract: Many vertebrate tissues, including skin, are known to develop as a consequence of epithelial-mesenchymal interactions. Much less is known about the role of cell-cell interaction within the epithelial or the mesenchymal compartments in morphogenesis. To investigate cell-cell interactions during skin development, and the potential role of the Notch homolog in this process, we cloned the mouse homolog of Notch (mNotch) and studied its expression pattern, starting as early as mesoderm formation. The novel application of double-labeled in situ hybridization in vertebrates allowed high resolution analysis to follow the fate of mNotch expressing cells directly. In comparison with the distribution of Id mRNA, analysis confirmed that in the hair follicle high levels of mNotch are expressed exclusively in the epithelial compartment. Hair follicle matrix cells start expressing mNotch as different cell types become distinguishable in the developing follicle. mNotch mRNA expression persists throughout the growth phase of the follicle and maintains the same expression profile in the second hair cycle. The cells in the follicle that undergo a phase of high level mNotch expression are in transition from mitotic precursors to several discreet, differentiating cell types. Our observations point out that both in time (during development) and in space (by being removed one cell layer from the dermal papilla) mNotch expression is clearly separated from the inductive interactions. This is a novel finding and suggests that mNotch is important for follicular differentiation and possibly cell fate selection within the follicle.

4/7/76 (Item 11 from file: 434)  
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci  
(c) 1998 Inst for Sci Info. All rts. reserv.

12270439 Genuine Article#: KY548 Number of References: 55  
Title: ALTERED EPIDERMAL GROWTH FACTOR-LIKE SEQUENCES PROVIDE EVIDENCE FOR A ROLE OF NOTCH AS A RECEPTOR IN CELL FATE DECISIONS  
Author(s): HEITZLER P; SIMPSON P  
Corporate Source: FAC MED STRASBOURG, CNRS, GENET MOLEC EUCARYOTES  
LAB, INSERM/F-67085 STRASBOURG//FRANCE//; FAC MED STRASBOURG, CNRS, GENET MOLEC EUCARYOTES LAB, INSERM/F-67085 STRASBOURG//FRANCE/  
Journal: DEVELOPMENT, 1993, V117, N3 (MAR), P1113-1123  
ISSN: 0950-1991

Language: ENGLISH Document Type: ARTICLE

Abstract: In Drosophila each neural precursor is chosen from a group of cells through cell interactions mediated by Notch and Delta which may function as receptor and ligand (signal), respectively, in a lateral signalling pathway. The cells of a group are equipotential and express both Notch and Delta. Hyperactive mutant Notch molecules, (Abruptex), probably have an enhanced affinity for the ligand. When adjacent to wild-type cells, cells bearing the Abruptex proteins are unable to produce the signal. It is suggested that in addition to the binding of Notch molecules on one cell to the Delta molecules of opposing cells, the Notch and Delta proteins on the surface of the same cell may interact. Binding between a cell's own Notch and Delta molecules would alter the availability of these proteins to interact with their counterparts on adjacent cells.

4/7/77 (Item 12 from file: 434)  
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci  
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12191586 Genuine Article#: KT999 Number of References: 43

Title: COMPLEX FUNCTION AND EXPRESSION OF DELTA DURING DROSOPHILA OOGENESIS  
Author(s): BENDER LE MOOH PJ; MUSKAVITCH MAT  
Corporate Source: INDIANA UNIV, DEPT BIOL, GENET CELL & DEV BIOL  
PROGRAM/BLOOMINGTON//IN/47405; INDIANA UNIV, DEPT BIOL, GENET CELL & DEV  
BIOL PROGRAM/BLOOMINGTON//IN/47405  
Journal: GENETICS, 1993, V133, N4 (APR), P967-978  
ISSN: 0016-6731

Language: ENGLISH Document Type: ARTICLE

Abstract: Delta (Dl) encodes a cell surface protein that mediates cell-cell interactions central to the specification of a variety of cell fates during embryonic and postembryonic development of *Drosophila melanogaster*. We find that the Delta protein is expressed intermittently in follicle cells and in germ-line cells during stages 1-10 of oogenesis. Furthermore, Delta expression during oogenesis can be correlated with a number of morphogenetic defects associated with sterility observed in Dl mutant females, including failure of stalk formation within the germarium and subsequent fusion of egg chambers, necrosis in germ-line cells, and multiphasic embryonic arrest of fertilized eggs. We have also identified a Dl mutation that leads to context-dependent defects in Dl function during oogenesis. Direct comparison of Delta protein expression with that of the Notch protein in the ovary reveals substantial, but incomplete, coincidence of expression patterns in space and time. We discuss possible roles for the Delta protein in cell-cell interactions required for cell fate specification processes during oogenesis in light of available developmental and histochemical data.

9/7/2 (Item 2 from file: 5)  
DIALOG(R)File 5:BIOSIS PREVIEWS(R)  
(c) 1998 BIOSIS. All rts. reserv.

13783785 BIOSIS Number: 99783785

Secreted forms of **DELTA** and **SERRATE** define antagonists of  
**Notch** signaling in *Drosophila*

Sun X; **Artavanis-Tsakonas S**

Howard Hughes Med. Inst., Dep. Cell Biology Biol., Boyer Cent. Molecular  
Med., Yale Univ., New Haven, CT 06536-0812, USA  
Development (Cambridge) 124 (17). 1997. 3439-3448.

Full Journal Title: Development (Cambridge)

ISSN: 0950-1991

Language: ENGLISH

Print Number: Biological Abstracts Vol. 104 Iss. 010 Ref. 141389

We examined the function of secreted forms of the two known *Drosophila*  
**Notch** ligands, **DELTA** and **SERRATE**, by expressing them under  
various promoters in the *Drosophila* developing eye and wing. The phenotypes  
associated with the expression of secreted **Delta** (DIS) or secreted  
**Serrate** (SerS) forms mimic loss-of-function mutations in the **Notch**  
pathway. Both genetic interactions between DIS or SerS transgenics and  
duplications or loss-of-function mutations of **Delta** or **Serrate**  
indicate that DIS and SerS behave as dominant negative mutations. These  
observations were extended to the molecular level by demonstrating that the  
expression of Enhancer of split m-**delta**, a target of **Notch**  
signaling, is down-regulated by SERS. The antagonistic nature of the two  
mutant secreted ligand forms in the eye is consistent with their behavior  
in the wing, where they are capable of down-regulating wing margin specific  
genes opposite to the effects of the endogenous ligands. This analysis  
uncover secreted molecular antagonists of **Notch** signaling and  
provides evidence of qualitative differences in the actions of the two

9/7/9 (Item 9 from file: 5)  
DIALOG(R)File 5:BIOSIS PREVIEWS(R)  
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8094782 BIOSIS Number: 91015782

DELTEX A LOCUS INTERACTING WITH THE NEUROGENIC GENES **NOTCH**  
**DELTA** AND MASTERMIND IN DROSOPHILA-MELANOGASTER

XU T; **ARTAVANIS-TSAKONAS S**

HOWARD HUGHES MEDICAL INST., DEP. CELL BIOL., YALE UNIVERSITY, NEW HAVEN,  
CONN. 06511.

GENETICS 126 (3). 1990. 665-678. CODEN: GENTA

Full Journal Title: Genetics

Language: ENGLISH

The **Notch** locus of *Drosophila melanogaster*, which codes for a transmembrane protein sharing homology with the mammalian epidermal growth factor, is one of a small number of zygotically acting genes, the so called neurogenic loci, which are necessary for the correct segregation of neural from epidermal lineages during embryogenesis. In an attempt to identify genes whose products may interact with that of **Notch**, we designed a genetic screen aimed at identifying suppressors of certain **Notch** mutations which are known to affect the extracellular epidermal growth factor homologous domain of **Notch**. Mutations in two neurogenic loci were identified as suppressors: **Delta**, whose product was recently shown to interact with **Notch** and mastermind. In addition, a third, X-linked gene was shown capable of acting as a suppressor. We show that this gene is the **deltex** locus, characterize the phenotype of **deltex** mutations, and demonstrate both a maternal and zygotic action of the locus. All **deltex** alleles behave as recessive viables affecting wing, ocellar and eye morphology. There are allele specific interactions between **deltex** and various **Notch** alleles; for example, **deltex** mutants with a reduced dosage of wild-type **Notch** die as pupae. **deltex** also interacts with **Delta** and mastermind in a fashion that is formally analogous to its interaction with **Notch**. These results emphasize the special relationship between **Notch**, **Delta** and mastermind suggested by previous work and indicate that **deltex** is likely to play an important role in the same genetic circuitry within which these three neurogenic loci operate.

9/7/10 (Item 10 from file: 5)  
DIALOG(R)File 5:BIOSIS PREVIEWS(R)  
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7660029 BIOSIS Number: 90028029

MOLECULAR INTERACTIONS BETWEEN THE PROTEIN PRODUCTS OF THE NEUROGENIC  
LOCI **NOTCH** AND **DELTA** TWO EGF-HOMOLOGOUS GENES IN DROSOPHILA

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HOWARD HUGHES MED. INST., DEP. CELL BIOL., YALE UNIV., NEW HAVEN, CT  
06511.

CELL 61 (3). 1990. 523-534. CODEN: CELLB

Full Journal Title: Cell

Language: ENGLISH

Genetic analyses have raised the possibility of interactions between the gene products of the neurogenic loci **Notch** and **Delta**, each of which encodes a transmembrane protein and EGF homology. To examine the possibility of intermolecular association between the products of these two genes, we studied the effects of their expression on aggregation in *Drosophila* S2 cells. We find that **Notch**-expressing cells form mixed



aggregates specifically with cells that express **Delta** and that this process is calcium dependent. In addition, we show that **Notch** and **Delta** can associate within the membrane of a single cell, and further, that they form detergent-soluble intermolecular complexes. Our analyses suggest that **Notch** and **Delta** proteins interact at the cell surface via their extracellular domains.

9/7/20 (Item 1 from file: 351)  
DIALOG(R)File 351:DERWENT WPI  
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011122234

WPI Acc No: 97-100159/199709

New vertebrate **Delta** protein, DNA and antibodies - for treating and preventing cancer, nervous system disorders and for tissue regeneration  
Patent Assignee: IMPERIAL CANCER RES TECHNOLOGY (IMCR ); UNIV YALE (UYA )

Inventor: **ARTAVANIS-TSAKONAS S**; GRAY G E; HENRIQUE D M P;

ISH-HOROWICZ D; LEWIS J H; HENRIQUE D; LEWIS J

Number of Countries: 021 Number of Patents: 002

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Main IPC	Week
WO 9701571	A1	19970116	WO 96US11178	A	19960628	C07H-017/00	199709 B
AU 9664817	A	19970130	AU 9664817	A	19960628	C07H-017/00	199720

Priority Applications (No Type Date): US 95589 A 19950628

Cited Patents: 3.Jnl.Ref

Patent Details:

Patent	Kind	Lan	Pg	Filing Notes	Application	Patent
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WO 9701571	A1	E	135			
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Designated States (National): AU CA JP US

Designated States (Regional): AT BE CH DE DK ES FI FR GB GR IE IT LU MC

NL PT SE

AU 9664817 A

Based on

WO 9701571

Abstract (Basic): WO 9701571 A

A purified vertebrate **Delta** protein (A) and functional analogues, derivs. and fragments are new. Also claimed are: (1) a fragment of (A) which is able to display one or more functional activities of human **Delta** protein; (2) a chimeric protein comprising a fragment of (A) of at least 20 amino acids fused via a covalent bond to a second protein, which is different to (A); (3) an antibody (Ab) which binds to (A) but does not bind to a *Drosophila* **Delta** protein; and (4) an isolated nucleic acid (I) encoding (A) or a fragment, or nucleic acid complementary to (I).

USE - (A), (I), Abs and mols. containing these are used therapeutically in compsns. to treat or prevent diseases or disorders, such as a malignancy characterised by increased **Notch** activity or expression, or cervical, breast, lung or colon cancer, melanoma or seminoma (claimed). (A) may also be used to treat a nervous system disorder or to promote tissue regeneration. The oligonucleotide inhibits the expression of (A) in a cell. (A) may be used to diagnose a disease or disorder by measuring the binding ability of a **Notch** protein to bind to (A), or by measuring the level of (A) in a patient relative to a normal person.. The Abs can be used to detect and quantitate (A) mRNA and protein.

Dwg.0/14

Derwent Class: B04; D16

International Patent Class (Main): C07H-017/00

International Patent Class (Additional): C07K-014/00; C12N-005/00;

C12N-015/00; C12P-021/06

9/7/23 (Item 1 from file: 358)  
DIALOG(R)File 358:Current BioTech Abs  
Royal Soc Chem & DECHEMA . All rts. reserv.

059550 CBA Acc. No.: 12-02-001238 DOC. TYPE: Patent

Binding domains in **Notch** and **Delta** proteins.

AUTHOR: **Artavanis-Tsakonas, S.**; Muskavitch, M. A. T.; Fehon, R. G.;  
Blaumueller, C. M.; Shepard, S. B.

CORPORATE SOURCE: Yale Univ.; Indiana Univ. Foundation, New Haven, CT  
06511; Bloomington, IN 47402, USA; USA

CODEN: PIXXD2

PATENT NUMBER: WO 9219734

PATENT APPLICATION: US 695189 (910503)

PUBLICATION DATE: 12 Nov 1992 (921112) LANGUAGE: English

ABSTRACT: Nucleotide sequences of the human **Notch** and **Delta** genes are provided as are amino acid sequences of their encoded proteins, or fragments thereof containing an antigenic determinant or which are functionally active. Adhesive fragments and sequences thereof are also provided as are proteins ("toporythmic proteins") encoded by toporythmic genes which mediate homotypic or heterotypic binding to toporythmic proteins. The toporythmic genes refer to the genes **Notch**, **Delta**, and Serrate, as well as to other members of the **Delta**/Serrate family. Antibodies to human **Notch** and to adhesive fragments are also given.

9/7/26 (Item 3 from file: 399)  
DIALOG(R) File 399:CA SEARCH(R)  
(c) 1998 American Chemical Society. All rts. reserv.

121026887 CA: 121(3)26887m PATENT  
Therapeutic and diagnostic methods and compositions based on Notch  
proteins and nucleic acids  
INVENTOR(AUTHOR): Artavanis-Tsakonas, Spyridon; Fehon, Richard Grant;  
Zagouras, Panayiotis; Blaumueller, Christine Marie  
LOCATION: USA  
ASSIGNEE: Yale University  
PATENT: PCT International ; WO 9407474 A1 DATE: 940414  
APPLICATION: WO 93US9338 (930930) \*US 955012 (920930) \*US 83590 (930625)  
PAGES: 232 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A61K-031/00A;  
A61K-031/70B; A61K-037/02B; A61K-039/44B; A61K-039/395B; C07H-021/04B;  
G01N-033/53B; G01N-033/68B DESIGNATED COUNTRIES: AU; BB; BG; BR; BY; CA;  
CZ; FI; HU; JP; KR; KZ; LK; LV; MG; MN; MW; NO; NZ; PL; RO; RU; SD; SK; UA;  
US; UZ; VN DESIGNATED REGIONAL: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT  
; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; ML; MR; NE; SN; TD;  
TG

SECTION:  
CA201006 Pharmacology  
CA209XXX Biochemical Methods  
IDENTIFIERS: human Notch protein therapeutic, cDNA antibody human Notch  
DESCRIPTORS:  
Gene, animal...  
cDNA, for human Notch protein and Drosophila Delta protein  
Deoxyribonucleic acid sequences, complementary...  
for human Notch protein and Drosophila Delta protein  
Alopecia... Cirrhosis... Intestine, neoplasm, colon, inhibitors... Keloid...  
Lung, neoplasm, inhibitors... Mammary gland, neoplasm, inhibitors... Neoplasm  
inhibitors, colon... Neoplasm inhibitors, lung... Neoplasm inhibitors, mammary  
gland... Neoplasm inhibitors, melanoma... Psoriasis...  
Notch protein as diagnostics and  
Proteins, specific or class, gene Delta...  
Notch protein as therapeutics in relation to  
Deoxyribonucleic acids, complementary, antisense...  
of human Notch gene, for diagnostics and therapeutics  
Protein sequences...  
of human Notch protein and Drosophila Delta protein  
Gene, animal, Serrate...  
protein of, Notch protein as therapeutics in relation to  
Antibodies... Antibodies, monoclonal...  
to human Notch protein, for diagnostics and therapeutics  
Testis, neoplasm, seminoma... Uterus, neoplasm, cervix...  
treatment and diagnosis of, Notch protein as diagnostics and

CAS REGISTRY NUMBERS:  
146636-21-7 amino acid sequence of  
156067-46-8 156067-47-9 156067-48-0 156067-49-1 156067-50-4  
156067-51-5 amino acid sequence of, therapeutics contg.  
146636-19-3 human Notch protein homologous to, as therapeutics  
148513-28-4 156067-52-6 156067-53-7 156067-54-8 156067-55-9 nucleotide  
sequence of  
146636-08-0 146636-13-7 156067-43-5 156067-44-6 156067-45-7 nucleotide

9/7/28 (Item 5 from file: 399)  
DIALOG(R) File 399:CA SEARCH(R)  
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118163654 CA: 118(17)163654k PATENT  
Binding domains in Notch and Delta proteins involved in their mutual  
interaction  
INVENTOR(AUTHOR): Artavanis-Tsakonas, Spyridon; Muskavitch, Marc Alan  
Telander; Fehon, Richard Grant; Rebay, Ilaria; Blaumueller, Christine Marie  
; Shepard, Scott Brockewell  
LOCATION: USA  
ASSIGNEE: Yale University; Indiana University Foundation  
PATENT: PCT International ; WO 9219734 A1 DATE: 921112  
APPLICATION: WO 92US3651 (920501) \*US 695189 (910503) \*US 791923 (911114)  
PAGES: 239 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12N-015/12A;  
C12N-015/63B; C12P-021/00B; C07K-013/00B DESIGNATED COUNTRIES: AU; BR; CA;  
FI; JP; KR; NO DESIGNATED REGIONAL: AT; BE; CH; DE; DK; ES; FR; GB; GR; IT  
; LU; MC; NL; SE  
SECTION:  
CA206003 General Biochemistry  
CA212XXX Nonmammalian Biochemistry  
CA213XXX Mammalian Biochemistry  
IDENTIFIERS: Notch Delta protein interaction Drosophila  
DESCRIPTORS:  
Gene, animal...  
cDNA, for Notch and Delta proteins of human, cloning and expression of  
Glycoproteins, specific or class, gene Notch, fusion products...  
chimeric gene for, expression in animal cell culture of, interaction  
with Delta protein in relation to  
Animal cell line, S2...  
expression in, of cDNAs for Notch and Delta proteins, interaction of  
proteins in relation to  
Deoxyribonucleic acid sequences, complementary...  
for Notch and Delta proteins of Drosophila and human and Serrate  
protein of Drosophila  
Proteins, specific or class, gene Delta...  
fusion products, chimeric gene for, expression in animal cell culture  
of, interaction with Notch protein in relation to  
Plasmid and Episome...  
hN3k, cDNA for human Notch protein on, cloning in Escherichia coli of  
Plasmid and Episome...  
hN4k, cDNA for human Notch protein on, cloning in Escherichia coli of  
Plasmid and Episome...  
hN5k, cDNA for human Notch protein on, cloning in Escherichia coli of  
Adhesion, bio-...  
induction of, by expression of Notch and Delta genes  
Glycoproteins, specific or class, gene Notch...  
interaction with Delta protein of and cloning of cDNA for human homolog  
of  
Proteins, specific or class, gene Serrate...  
interaction with Delta protein of, identification of domains involved  
in  
Proteins, specific or class, gene .delta....  
interaction with Notch protein of and cloning of cDNA for human homolog  
of  
Gene, animal, Notch...  
of Drosophila, expression in animal cell culture of, identification of  
Delta interacting domains in  
Gene, animal, Delta...

of Drosophila, expression in animal cell culture of, identification of  
Notch interacting domains in  
Protein sequences...  
of Notch and Delta and Serrate proteins of Drosophila  
Plasmid and Episome...  
pMTD11, Delta protein cDNA on, expression in S2 cells of  
Plasmid and Episome...  
pMtNMg, Notch protein cDNA on, expression in S2 cells of  
Antibodies...  
to Notch and Delta and Serrate proteins of Drosophila  
CAS REGISTRY NUMBERS:  
146636-25-1 amino acid sequence of  
146636-19-3 amino acid sequence of and role in interaction with Delta  
protein of  
146636-21-7 amino acid sequence of, complete, and expression in cell  
culture of cDNA for  
146636-26-2 amino acid sequence of, in interaction with Delta and Notch  
proteins  
7440-70-2 biological studies, in interaction of Notch and Delta proteins  
146636-22-8 in interaction with Notch and Serrate proteins  
146636-06-8 146636-07-9 146636-08-0 146636-09-1 146636-10-4  
146636-11-5 146636-12-6 146636-13-7 146636-14-8 146636-15-9  
146636-16-0 146636-17-1 146636-18-2 nucleotide sequence and cloning  
in Escherichia coli of  
140085-10-5 146636-23-9 146636-24-0 nucleotide sequence of  
146636-20-6 nucleotide sequence of, complete, and expression in cell  
culture of

9/7/30 (Item 2 from file: 434)  
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci  
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11183268 Genuine Article#: GN927 Number of References: 45

Title: CHOOSING A CELL FATE - A VIEW FROM THE **NOTCH** LOCUS

Author(s): **ARTAVANISTSAKONAS S**; SIMPSON P

Corporate Source: YALE UNIV, HOWARD HUGHES MED INST, DEPT CELL BIOL/NEW  
HAVEN//CT/06520; YALE UNIV, HOWARD HUGHES MED INST, DEPT BIOL/NEW  
HAVEN//CT/06520; FAC MED STRASBOURG, INSERM, CNRS, UNITE BIOL MOLEC GEN  
GENET 184, GENET MOLEC LAB/F-67085 STRASBOURG//FRANCE/

Journal: TRENDS IN GENETICS, 1991, V7, N11-1, P403-408

Language: ENGLISH Document Type: REVIEW

Abstract: During the development of *Drosophila melanogaster*, individual cells must make choices between a restricted set of possible fates in order to give rise to spatial patterns composed of different types of differentiated cells. The **Notch** locus appears to play a central and general role in the regulative events that control the local architecture of the final cellular pattern in several tissues, among